Preparative conversion of oximes to parent carbonyl compounds by cerium(IV) oxidation¹

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Oximes and semicarbazones are oxidized by ceric ammonium nitrate to the parent carbonyl compound in good yield. Suitable solvent systems include aqueous alcohols, acetonitrile, and acetic acid. The reaction is rapid at 0° or below. This procedure for regeneration of aldehydes and ketones from these derivatives may be preferable to the well-known hydrolytic procedures in some cases. The stoichiometry of the reaction was studied by isothermal calorimetry; two equivalents of oxidant are consumed by one mole of oxime evolving approximately 40 kcal/mole. A smaller consumption of oxidant by hexane-2,5-dione dioxime was attributed to stabilization of the monoxime as a nitroso chelate. Gaseous products were studied by infrared spectroscopy and nitrous oxide was identified as the sole product absorbing between 3 and 15 μ . A reaction mechanism is proposed involving one-electron oxidation to the iminoxy radical, oxidized by a second one-electron step to the α -hydroxy nitroso compound. Dimerization and elimination of hyponitrous acid gives the carbonyl compound. Nitrocyclohexane was absent from the oxidation product from cyclohexanone oxime. Carvone oxime was oxidized to carvone without racemization or significant attack of the olefin groups.

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Introduction

The formation of oxime and semicarbazone derivatives is a common method of isolating, purifying, identifying, and characterizing carbonyl compounds. This is especially true with natural products, for example the separation of ketone hormone intermediates obtained by oxidation of sterols may be done by formation of the sparingly soluble semicarbazones (1). After purification the regeneration of the original ketone or aldehyde is then encountered.

A number of good procedures exist including direct acid hydrolysis (2), acid-catalyzed exchange with pyruvic acid (1), levulinic acid (6) or formaldehyde (7), nitrous acid in acetic acid (8– 10), and most recently cleavage with bisulfite (11). These procedures are all hydrolytic and several involve equilibrium reaction of hydroxylamine with a more reactive carbonyl compound. They may take a number of hours to go to equilibrium or completion. Common hydrolytic procedures especially applicable to semicarbazones include sulfuric acid in ethanol (2), sulfuric acid in dioxane (3, 4) hydrochloric and acetic acids (5), and sodium nitrite and acetic acid (8). Some of the procedures are drastic and can lead to condensation products or hydrolysis of sensitive protecting groups such as acetoxy groups.

There are occasions when a mild procedure is

required which is quick and will not affect other groups present in the molecule. We believe a fast, mild, and usually satisfactory procedure has now been found in the oxidation of oximes and semicarbazones by cerium(IV).

Diaper and Richardson (12) have used the discharge of alcohol – ceric ammonium nitrate orange colors as a colorimetric quantitative determination method for oximes and other easily oxidized compounds. There has been some literature on oxime oxidations but when carbonyl compounds have been recovered the yield is poor (13).

Oxidants of the donor or peroxide type give nitro compounds. Thus oxidations with manganese dioxide in acetic acid (14, 15) result in high yields of the nitro compound. Employing trifluoroacetic acid and hydrogen peroxide results also in 50–80% yields of the nitro compounds (16, 17). Recently much work has been done on the electron spin resonance identification of iminoxy radicals produced by oxime oxidation, the usual oxidant being lead tetraacetate (18–24), although ceric ammonium nitrate in methanol has also been used (19).

Ceric ammonium nitrate as an oxidant has attracted considerable attention lately. It can be used in aqueous solutions and partly organic solutions including aqueous acetic acid. It may be used in aqueous alcohols if the temperature is kept low to minimize attack on the solvent itself. Its power as an oxidant is evident from the fact

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that the standard redox potential of Ce(IV)-Ce(III) is approximately 1.6 V. An interesting feature of its use as a preparative oxidant is the ability to oxidize benzyl alcohols smoothly to benzaldehydes (25) without significant further oxidation of the aldehyde to the aromatic acid. It was this fact and the earlier colorimetric work which recommended this reagent to our attention.

In our procedure low reaction temperatures were employed, but the solubility of the oxime or semicarbazone in the solvent became a factor limiting the temperature. Choice of solvents other than alcohols is limited by considerations of low-temperature solubility of reagent and substrate. Reactions were rapid and easy to follow, because the color was discharged or diminished and vigorous gas evolution occurred for a few minutes. Transient blue colors were often seen. After dilution with water, the carbonyl compound was recovered by solvent extraction.

Experimental

Solutions were concentrated under reduced pressure below 50° in a rotating evaporator. Melting points were determined on a Fisher-Johns hotstage apparatus and are uncorrected. Infrared (i.r.) spectra were determined using a Perkin-Elmer Infracord model 137. Nuclear magnetic resonance (n.m.r.) spectra were obtained using samples in CDCl₃ containing 6% of tetramethylsilane as an internal standard. The instrument was a Varian A-60-A spectrometer. Gas-liquid chromatography (g.l.c.) was performed on a Burrell "Kromotog" model KD gas chromatograph with a thermal conductivity detector. Columns were constructed of $\frac{3}{16}$ in. copper tubing 20 ft. long coiled with a diameter of approximately 4 in. The liquid phase was Carbowax 4000, 5% on Chromosorb P (60-80 mesh). Helium flow rates of 45-110 ml/min and temperatures of 105-170 °C were employed. Columns were conditioned for at least 18 h at 190° before use.

The internal standard method was used in the determination of the yields of recovered aldehydes and ketones. An appropriate ketone with a symmetrical, well resolved peak eluting reasonably close to the peak of interest was selected as an internal standard: thus cycloheptanone was used for determination of *d*-camphor or cyclohexanone yields, *d*-camphor for *l*-carvone, and cyclohexanone for cycloheptanone and heptaldehyde. Peak areas were measured by multiplying the peak height by the width at the middle.

A study of the stoichiometry of the reaction was made using an isothermal calorimeter. It was an all-glass ice calorimeter similar to that described by Vallee (26). In principle the reaction takes place in a tube surrounded by ice. Melting of the ice mantle causes a mercury meniscus to move along a graduated horizontal capillary, whose calibration, determined electrically, corresponded to 1.23 cal/cm. The aqueous solution of ceric ammonium nitrate (0.2–0.7 *M* in *N* HNO₃) was initially pipetted

into the vessel containing methanol (25 ml) at 0°. A solution of the oxime in absolute alcohol of known concentration was sealed into a weighed fragile glass bulb and introduced. A steady drift (fore-drift) of approximately 0.1 cal/min was observed. The bulb was broken with a stirrer and rapid evolution of heat observed. At the end of 30-40 min the rate of drift (after-drift) was usually about the same as that of the fore-drift. The heat evolution was measured by finding the difference between the extrapolated fore-drift and after-drift lines at the time of mixing. Blanks (0.3-0.5 cal) were determined and subtracted from the heat measured (30-40 cal per determination). Results were expressed graphically for cyclohexanone oxime (Fig. 1) and heptaldoxime (Fig. 2). Benzophenone oxime similarly gave a graph indicating consumption of 1.87 equivalents of oxidant per mole evolving 39.8 kcal/mole. Hexane-2,5-dione dioxime used 3.47 equivalents or 1.735 equivalents of oxidant per oxime group; the evolved heat was 19 kcal per equivalent of Ce(IV). In all isothermal calorimeter experiments, solutions were so dilute that gas evolution did not occur.

Preparation of Oximes and Semicarbazones

Heptaldoxime was a commercial sample (Eastman No. 3001) and had constants in agreement with literature values. Other oximes were prepared from the carbonyl compound and hydroxylamine hydrochloride in aqueous or aqueous-alcoholic basic media as appropriate. Semicarbazones were similarly prepared using semicarbazide hydrochloride. Melting points agreed with literature values; α -*l*-carvoxime had m.p. 74-75° and $[\alpha]_{\rm D}^{22}$ - 39.1° (1.98 g in 18.88 g of 95% ethanol). Wallach (27) found m.p. 73.5°, $[\alpha]_{\rm D}^{19}$ - 43.5° (1.9799 g in 18.8826 g of 95% ethanol).

Oxidation of Oximes and Semicarbazones

In a typical experiment the oxime or semicarbazone (5 mmoles) was dissolved in ethanol (20 ml) and cooled



FIG. 1. Heat liberated in the reaction of ceric ammonium nitrate with cyclohexanone oxime.

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FIG. 2. Heat liberated in the reaction of ceric ammonium nitrate with heptaldoxime.

to the reaction temperature. The oxidant was prepared by mixing 20 mmoles (100% excess) of aqueous ceric ammonium nitrate (0.3 M in 0.5 or 1.0 N HNO₃, 67 ml) at 0 °C with ethanol at -40° and adjusting to the desired reaction temperature. A little care must be taken to avoid precipitation of ceric ammonium nitrate. The ceric solution was then mixed with the oxime solution, stirred manually, and maintained at the reaction temperature for 5 min. The mixture was diluted with an equal volume of ice water and immediately extracted with chloroform or other immiscible solvent (e.g. three portions of 50 ml). Extracts were dried over anhydrous MgSO₄, filtered, and the solvent was removed by distillation at atmospheric pressure. The yields of carbonyl compounds are summarized in Table I. Oxidation temperatures, solvents, and isolation methods were varied to attempt to optimize yields. Results are given in Table II.

Oxidation of Carvone Oxime

Carvone oxime (0.826 g, 5 mmoles) was dissolved in ethanol and cooled to -20° . To this was added the ceric oxidant solution prepared by mixing ceric ammonium nitrate (0.3 *M* in 0.5 *N* HNO₃, 40 ml, 10.2 meq) with ethanol (95%, 50 ml) at -40° C and adjusted to -20° C. The reaction mixture was held at $-20\pm2^{\circ}$ for 5 min then diluted with an equal volume of cold water and extracted immediately with pentane (three portions of 75 ml). The organic layer was washed with saturated sodium bicarbonate solution, water, dried (MgSO₄), and filtered. After removal of the pentane by distillation

the resultant solution was divided into aliquots and analyzed by g.l.c. The average yield was 71 %.

In a separate experiment to examine the purity of the recovered carvone the proportions of reactants above were doubled and the same procedure followed except that the pentane was removed by rotary evaporation below 40 °C. The resulting liquid was distilled at 10 mm and approximately 108 °C in a short-path distillation apparatus. The carvone had $[\alpha]_{D}^{24} - 54.2^{\circ}$ (c, 2.60, 95% ethanol). A sample of the carvone starting material was purified by vacuum distillation (123–125 °C, 33 mm) and found to have $[\alpha]_{D}^{24} - 54.9^{\circ}$ (c, 2.611, 95% ethanol). The n.m.r. spectra of the two carvone samples were identical with each other and with the published spectrum.

Examination of the Gaseous Product

Cyclohexanone oxime (10 mmoles) in 50% aqueous acetic acid (100 ml) was placed in a flask fitted with a dropping funnel and gas inlets and outlets. The solution was cooled to 0 °C and stirred magnetically while a solution of ceric ammonium nitrate (134 ml, 40 mmoles, 0.3 M in N HNO₃) was added dropwise. A stream of hydrogen was passed through the mixture to sweep out volatile products. They passed first into a trap cooled in solid CO₂/acetone and then into a trap cooled in liquid air (N₂O boils at -90°). After addition of the oxidant was complete (30-40 min) the reaction mixture was warmed to room temperature while stirring continued. One hour later the hydrogen stream was interrupted. The trap, cooled in liquid air, was connected to a gas cell for use with the i.r. spectrometer and flushed with hydrogen. This cell had NaCl windows 10 cm apart. The trap was allowed to warm slowly to room temperature and the volatilized contents were displaced by hydrogen into the cell. The spectrum had strong sharp absorption peaks at 4.48, 4.55, 7.75, and 7.9 μ . There were no other peaks. Similar peaks were seen in the spectra of the volatile products from cyclopentanone oxime and acetophenone oxime and from cyclohexanone oxime oxidized by ceric ammonium nitrate made up in aqueous acetic acid in place of nitric acid. A control experiment was

TABLE I

Cerium(IV) oxidation of oximes and semicarbazones

Oxime of	Ketone yield (%)§
Cyclohexanone	88
Cyclopentanone	83
Camphor	27
Carvone	71
Cycloheptanone	82
Acetophenone	90†, 74*
Heptanal	72±
Benzophenone	79*
Semicarbazone of	
Cycloheptanone	81
Cyclohexanone	78
*By weight of 2,4- formed.	dinitrophenylhydrazone

[†]Vacuum distilled and weighed.

Aldehyde yield. §Yield determined by g.l.c.

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TABLE II Oxidation conditions

Compound	Temperature (°C)	Solvent	Isolation method¶	Ketone yield (%)*
Cyclohexanone oxime	-15 to -20	EtOH	A,B	77-80
	0	EtOH	A,B	73-81
	-20 to -30	MeOH	A,B	74, 82
	-15 to -20	EtOH	A,C	80-84
	-7 to -12	EtOH	A,C	88
	-7 to -12	CH₃CN	A,C	65–72
	-7 to -12	$CH_{3}CN$	D,C	32–35
	-15 to -20	EtOH	A,B^{\dagger}	78-78.5
Cycloheptanone oxime	-12 to -17	EtOH	A,C	75–82
Acetophenone oxime	-10 to -15	EtOH	A,C,E	90‡,§
Heptaldoxime	-5 to -10	EtOH	A,C	25-27
-	0 to 4	EtOH	A,C	49
	0 to 2	CH₃CN	A,C	49–55
	0 to - 4	CH₃CN	D,C	69 - 75
Carvone oxime	-10	EtOH	A,C	62-63
	0	EtOH	A,C	66-66.5
	-20	EtOH	D,C	70–72§
Cyclopentanone oxime	-20	MeOH	A,B	83 °
Cycloheptanone semicarbazone	-5 to -10	EtOH	A,C	79.5-82.5
Cyclohexanone semicarbazone	-12 to -17	EtOH	A,C	74-81

*Yield determined by g.l.c. except where noted. †Oxidation by 0.295 *M* ceric ammonium nitrate in 0.5*N* acetic acid. ‡Yield determined by weight of recovered product. \$An n.m.r. spectrum was indistinguishable from the spectrum of an authentic sample. [[Aldehyde yield. ¶Nort: A, chloroform extraction; B, rotary evaporated below 30 °C; C, solvent removed by distillation; D, pentane extraction; E, product purified by vacuum distillation.

performed by flushing the cell with hydrogen and introducing authentic nitrous oxide from a cylinder. The spectrum was identical with that of the oxime product.

Results and Discussion

In most cases a reasonable recovery of carbonyl compound from the oxime or semicarbazone was obtained. Low yields from camphor oxime may be attributable to steric hindrance. The Ce(IV)

oxidant appears to differ from oxidants of the donor type in that nitroalkane formation was not observed, and, for the cyclohexanone oxime case, it was shown by g.l.c. to be entirely absent. Identification of nitrous oxide evolved, earlier work on iminoxy radical formation, observation of blue-green colors, and the observed stoichiometry of two electrons per oxime group lead us to propose the reaction mechanism scheme outlined:



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The iminoxy radical known to be the first product of oxime oxidation, is produced in a one-electron step, so a second oxidation process, involving one electron per mole, must be postulated. Hybridization of the radical has been discussed by other authors. The radical can be oxidized to a cation having a canonical structure positively charged on the carbon atom. The hydroxy-nitroso intermediate 2 has not been isolated, but an analogous compound, 4-t-butyl-1-acetoxy-1-nitrosocyclohexane, was observed by Lown (23) in the oxidation of 4-t-butylcyclohexanone oxime by lead tetraacetate. It was obtained as a blue oil and a white crystalline dimer. Compound 2 would dimerize to 3 shown in the trans type of structure discussed by Gowenlock (28) for dimeric unsubstituted nitroso-hydrocarbons. An α-hydroxy-nitroso compound, monomer or dimer, is analogous to other α -hydroxy chlorides and gem diols. By analogy with them, easy decomposition would be expected and could take place as shown to give hyponitrous acid (4) and the carbonyl compound. Compound 4 is a postulated intermediate in the oxidation of hydroxylamine itself to nitrous oxide.

Dimerization of the iminoxy radical through the oxygen atoms would not lead to nitrous oxide but to a peroxide; dimerization through nitrogen would violate the adjacent charge rule. Such mechanisms are therefore discarded. Another possible mechanism, hydrolysis to hydroxylamine and oxidation of the latter, is considered unlikely since oxime hydrolysis is known to be a much slower process than the oxidative cleavage studied.

While the examples given in the Tables are drawn from aliphatic, alicyclic, or aromatic classes, the reaction may be general. The carvone oxime experiment shows that it is possible for good recovery of the ketone to be achieved when the molecule contains other oxidizable groups. Moreover, retention of most of the optical activity indicated that the conditions of the reaction are sufficiently mild for general application in natural product work.

Semicarbazones in general are less rapidly oxidized than oximes and their lower solubility poses problems in the choice of solvent and conditions. The inorganic products of semicarbazone oxidation were not studied.

The stoichiometry of the oxidation was ob-

served by isothermal calorimetry and indicated consumption of two equivalents of oxidant per mole of oxime. Slightly more than two equivalents for cyclohexanone (Fig. 1) was absorbed because of further attack on the ketone. Heptaldehyde (Fig. 2) also showed evidence of two or more simultaneous reactions in the isothermal calorimeter. The break in the curve was in the vicinity of two electrons per mole, but for high oxime to oxidant ratios the heat liberation increased. A similar slight rise, though less steep, was seen in the hexane-2,5-dione dioxime curve and consumption of the oxidant was less than two electrons per oxime group. No product isolation study was made in this case, but the solution was seen to have a strong and unusually persistent blue color. It would be expected that the product of the first stage of oxidation having one keto and one oximino group would be stabilized as structure 5 and possibly resist further oxidation.



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